COMPOSITIONS AND METHODS FOR TARGETED CYTOKINE DELIVERY

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. application Ser. No. 16/075,069, filed Aug. 2, 2018, PCT application number PCT/US2017/016688, filed Feb. 6, 2017, U.S. Provisional Application No. 62/292,046, filed Feb. 5, 2016, U.S. Provisional Application No. 62/342,630, filed May 27, 2016, U.S. Provisional Application No. 62/350,056, filed Jun. 14, 2016, and U.S. Provisional Application No. 62/419,146, filed Nov. 8, 2016, each of the disclosures of which is hereby incorporated by reference in its entirety.

GOVERNMENTAL RIGHTS

[0002] This invention was made with government support under A1073552, A1019687, AI109948, HHSN272201200026C and HL113931 awarded by the National Institutes of Health. The government has certain rights in the invention.

FIELD OF THE INVENTION

[0003] The present disclosure encompasses compositions and methods for targeted delivery of cytokines and for recruiting immune cells to target cells. Through specific delivery of cytokines and other agents, the compositions disclosed herein may improve immunotherapy and in some instances, limit side effects associated with immunotherapy.

BACKGROUND OF THE INVENTION

[0004] Systemic administration of high dose interleukin 2 (IL2) is one of the most potent forms of immunotherapy and is currently approved by the FDA for treatment of several malignancies. Efficacy of this treatment depends on activating cytotoxic lymphocytes (CTLs) such as natural killer cells (NK) and $CD8^+$ T lymphocytes ($CD8^+$ CTLs). Clinical trials have demonstrated approximately 15% partial or complete tumor responses, with up to 5% of patients having a durable long-lasting response resembling a cure. Despite these encouraging results in a minority of patients, most do not achieve a benefit or stop IL2 therapy prematurely due to complications such as blood pressure changes and pulmonary or systemic capillary leak. It is thought that the direct action of IL2 on vascular endothelium contributes to the majority of these side effects. The efficacy of IL2 is also limited by preferential activation of $CD4^+$Foxp3+ regulatory T cells (T_{regs}), which decrease the tumor immune response. For these reasons treatment with high-dose IL2 has fallen out of favor clinically.

[0005] Side effects and deceased efficacy of IL2 therapy occur due to the high affinity trimeric $\alpha\beta\gamma$ IL2 receptor (IL2R), which is expressed by vascular endothelial cells and T_{regs} at baseline. Thus $CD4^+Foxp3^+$ T_{regs} and vascular endothelium are activated at much lower doses of IL2 than NK cells, which express the lower affinity $\beta\gamma$ chains of the IL2R at rest. NK cells do express the high affinity α chain of IL2R after activation and depend on this trimeric receptor for peak cytolytic capacity. Mutant forms of IL2 with decreased affinity for IL2Rα have been described and offer a more favorable side effect profile. However, they also result in lower efficacy and decreased therapeutic potential due to decreased CTL activation. Therefore, there is a need in the art for a form of IL2 that could preferentially bind to and activate CTLs without activating T_{regs} and endothelial cells. Such an IL2 derivative might overcome such clinical barriers and result in more efficacious immunotherapy with fewer side effects.

SUMMARY OF THE INVENTION

[0006] In an aspect, the disclosure provides a composition comprising a cytokine linked to a NKG2D ligand. In one particular embodiment, the NKG2D ligand is an anti-NKG2D antibody.

[0007] In another aspect, the disclosure provides a composition comprising a ligand to the NKG2D receptor and a targeting molecule. The targeting molecule directs the composition to a binding partner on a target cell and recruits an immune cell upon the ligand specifically binding to the NKG2D receptor on the immune cell. In one instance, the ligand is orthopoxvirus major histocompatibility complex class I-like protein (OMCP). The targeting molecule can be linked to the ligand or unlinked and presented together in a single composition with the ligand or administered concurrently in separate compositions.

[0008] In another aspect, the disclosure provides a method to deliver a cytokine to a target cell comprising contacting a target cell with a composition comprising a cytokine linked to a NKG2D ligand. In still another aspect, the disclosure provides a method to activate immune cells comprising contacting an immune cell with a composition comprising a proinflammatory cytokine linked to a NKG2D ligand. The ligand specifically binds to a receptor on the immune cell thereby activating the cell.

[0009] In still another aspect, the disclosure provides a method to recruit and activate immune cells at a particular target cell comprising providing a composition comprising a ligand to an NKG2D receptor and a targeting molecule.

[0010] In still yet another aspect, the disclosure provides a method to treat a tumor comprising identifying a subject with a tumor and administering to the subject a therapeutically effective amount of a composition comprising a proinflammatory cytokine linked to a NKG2D ligand.

[0011] In a different aspect, the disclosure provides a method to treat a viral infection comprising administering to the subject a therapeutically effective amount of a composition comprising a proinflammatory cytokine linked to a NKG2D ligand. In other aspects, the disclosure provides a chimeric peptide comprising a cytokine peptide and a NKG2D ligand peptide.

[0012] In certain aspects, the disclosure provides a chimeric peptide comprising a cytokine peptide and an anti-NKG2D antibody.

[0013] In another aspect, the disclosure provides a composition comprising a cytokine linked to a programmed cell death protein 1 (PD1) ligand. In one particular embodiment, the PD1 ligand is programmed cell death ligand 1 (PDL1). In another particular embodiment, the PD1 ligand is programmed cell death ligand 2 (PDL2).

[0014] In another aspect, the disclosure provides a method to deliver a cytokine to a target cell comprising contacting a target cell with a composition comprising a cytokine linked to a PD1 ligand. In still another aspect, the disclosure provides a method to activate immune cells comprising contacting an immune cell with a composition comprising a